GUIDANCE FOR INDUSTRY

FOR THE SUBMISSION OF AN ENVIRONMENTAL ASSESSMENT IN HUMAN DRUG APPLICATIONS AND SUPPLEMENTS

Center for Drug Evaluation and Research (CDER)

November 1995

CMC 6

TABLE OF CONTENTS

I. INTRODUCTION 1

II. WHEN IS AN ACTION CATEGORICALLY EXCLUDED? 2

III. PREPARING AN EA FOR SUBMISSION TO CDER 3

A. When is an EA or AEA required under the regulations? 3

1. NDA's 4

2. NDA Supplements 4

3. ANDA/AADA's 4

4. IND's 5

B. What type of EA should be submitted? 5

1. Infrequent Use AEA's 5

2. Naturally Occurring Substances AEA's 6

3. AEA's for Products Approved by EPA 6

C. What EA information should be provided in an application? 7

D. Content and Format 7

1. Date 7

2. Name of Applicant/Petitioner 7

3. Address 7

4. Description of Proposed Action 8

a. Requested Approval 8

b. Need for Action 8

c. Production Locations 8

d. Locations of Use 9

e. Disposal Sites 9

5. Identification of Chemical Substances that are the Subject of the Proposed Action 10

a. Nomenclature 10

i. Established Name (U.S. Adopted Name-USAN) 10

ii. Brand/Proprietary Name 10

iii. Chemical Names 10

b. Chemical Abstracts Service (CAS) registration number 11

c. Molecular Formula 11

d. Molecular Weight 11

e. Structural (graphic) Formula 11

f. Physical Description 11

g. Additives 11

h. Impurities 11

6. Introduction of Substances into the Environment 12

a. Substances Expected to be Emitted 12

b. Controls Exercised 12

c. Citation of and Statement of Compliance with Applicable Emission Requirements 12

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements 13

e. Expected Introduction Concentrations 13

i. Expected Introduction Concentration from Use . 14

ii. Expected Introduction Concentration from Disposal 15

7. Fate of Emitted Substances in the Environment 15

a. Tiered Approach to Determining Environmental Fate (EA format item 7) and Effects (EA format item 8 15

b. Type of Fate Information to be Submitted 17

i. EA's filed pursuant to 21 CFR § 25.31a(a) 17

ii. EA's filed pursuant to 21 CFR § 25.31a(b)(3) 17

iii. EA's filed pursuant to 21 CFR § 25.31a(b)(5) 17

iv. EA's filed pursuant to 21 CFR § 25.31a(b)(6) 18

c. Tier 0 18

d. Fate information to be submitted for an EA filed pursuant to 21 CFR § 25.31a(a) 19

i. Identification of Substances of Interest 19

ii. Physical/Chemical Characterization 19

iii. Environmental Depletion Mechanisms 20

iv. Expected Environmental Concentration (EEC) . . 21

v. Summary 21

8. Environmental Effects of Released Substances 22

9. Use of Resources and Energy 26

a. Natural Resources and Energy 26

b. Effect on Endangered or Threatened Species 26

c. Effect on Property Listed in or Eligible for Listing in the National Register of Historic Places 26

10. Mitigation Measures 26

11. Alternatives to the Proposed Action 27

12. List of Preparers 27

13. Certification 27

14. References 28

15. Appendices 28

E. Data Summary Table 28

F. Test Methods and Report Formats 28

G. Confidential/Non-Confidential Information 29

IV. EA'S INVOLVING BIOTECHNOLOGY PRODUCTS 29

V. EA'S INVOLVING DRUGS DERIVED FROM NATURAL RESOURCES 30

VI. FOREIGN MANUFACTURING FACILITIES 31

VII. DRUG MASTER FILES 31

VIII. REFERENCES 32

ATTACHMENT A A-1

ATTACHMENT B B-1

ATTACHMENT C C-1

ATTACHMENT D D-1

ATTACHMENT E E-1

GUIDANCE FOR INDUSTRY[1]

FOR THE SUBMISSION OF AN ENVIRONMENTAL ASSESSMENT IN HUMAN DRUG APPLICATIONS AND SUPPLEMENTS

I. INTRODUCTION

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impacts of their actions and to ensure that the interested and affected public is informed of environmental analyses. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving drug product applications as an integral part of its regulatory process. FDA's regulations in 21 CFR Part 25 specify that environmental assessments (EA's) or abbreviated environmental assessments (AEA's) must be submitted as part of certain new drug applications (NDA's), antibiotic applications, abbreviated new drug applications (ANDA's), abbreviated antibiotic applications (AADA's), investigational new drug applications (IND's) and for various other actions (see 21 CFR § 25.22(a)).

This guidance provides information on how to prepare EA's for submission to the Center for Drug Evaluation and Research (CDER) for these drug product applications. Topics covered include: 1) when categorical exclusions apply; 2) when to submit an EA or AEA; 3) the content and format of EA's or AEA's; 4) approaches to determining the environmental fate and effects of substances; 5) test methods; 6) treatment of confidential information submitted in support of an EA; 7) special considerations associated with EA's for genetically altered organisms and materials and products

---

[1] This guidance has been prepared under the auspices of the Office of Pharmaceutical Science of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. The guidance is an informal communication under 21 CFR § 10.90(b)(9) that reflects the best judgment of CDER employees at this time. It does not create or confer any rights, privileges or benefits for or on any person, nor does it operate to bind or obligate FDA in any way. For further information about this guidance, contact Nancy B. Sager, Center for Drug Evaluation and Research, HFD-357, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-594-6740; FAX: 301-594-6197, Internet: SAGERN@CDER.FDA.
GOV). For additional copies of this guidance contact the Consumer Affairs Branch, HFD-210, Center for Drug Evaluation and Research, 7500 Standish Place, Rockville, MD, 20855, 301-594-1012. An electronic version of this guidance is also available via Internet by connecting to the CDER file transfer protocol (FTP) server (CDVS2.CDER.FDA.GOV).

derived from natural sources; 8) EA documentation for foreign manufacturing facilities; and 9) Drug Master Files (DMF's).

Information in this guidance, in addition to the Code of Federal Regulations (CFR) and the FDA EA Technical Handbook (NTIS Publication Number PB 87 175345/AS) which provides information on acceptable test methods, represents the core information available from CDER to assist industry in preparing an EA.

Under the President's reinventing government (REGO) initiatives announced in April, 1995, CDER is reevaluating its environmental regulations and plans to revise the regulations to reduce the number of EA's required to be submitted by industry and, consequently, the number of finding of no significant impacts (FONSI's) prepared by the agency under NEPA. FDA will issue for public comment a notice of proposed rulemaking that will propose additional categorical exclusions for those actions CDER has determined normally do not individually or cumulatively have a significant effect on the quality of the human environment. This guidance, explaining how to prepare an EA when required by current regulations, will remain in effect until superseded by revised final regulations or new CDER guidance.

II. WHEN IS AN ACTION CATEGORICALLY EXCLUDED?

Certain actions are subject to categorical exclusion and, therefore, ordinarily do not require the preparation of an EA because, as a class, these actions will not normally have significant effects on the environment (21 CFR § 25.24).

Submissions to CDER that are ordinarily categorically excluded under the regulations are actions on the majority of: 1) ANDA's and AADA's; 2) NDA supplements; and 3) IND's. ANDA's/AADA's and NDA supplements are categorically excluded from the requirement for preparation of an EA if they meet certain criteria (21 CFR 25.24(c)). The criteria include that the drug product will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect, and if data available to the agency do not establish that, at the expected levels of exposure, the substance may be toxic to organisms in the environment. In such cases, no EA or AEA need be submitted unless the agency has sufficient evidence to establish that the specific proposed action may significantly affect the quality of the human environment. Supplements for chemistry, manufacturing and controls changes, such as manufacturing site changes, typically meet the categorical exclusion criteria.

Action on an IND is categorically excluded from the requirement for preparation of an EA (21 CFR § 25.24(c)(4)) if the drug shipped under such notice is intended to be used for clinical studies or research in which waste will be controlled or the amount of waste expected to enter the environment may reasonably be expected to be nontoxic**.**

When requesting a categorical exclusion, the applicant should cite the categorical exclusion used and certify that the drug product meets the criteria for the categorical exclusion defined in the regulations. An applicant ordinarily need not provide data to demonstrate that it qualifies for a categorical exclusion. CDER will deny a categorical exclusion, however, and require an EA if there is sufficient available information that suggests that the substance may be toxic to organisms in the environment at the expected levels of exposure. Available information includes information submitted as part of the application as well as data available to the agency on the same or similar drugs. CDER will request additional information when warranted. If an applicant has information that indicates that a substance may be toxic to organisms in the environment at the expected level of exposure, the information should be provided to CDER.

CDER considers any action that, directly or indirectly, affects a species or the critical habitat of a species determined under the Endangered Species Act (ESA) or the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES) to be endangered or threatened, or that affects properties listed in or eligible for listing in the United States' Register of Historic Places, to be an action that may significantly affect the quality of the human environment. For such actions, CDER may request additional information if a categorical exclusion is claimed.

III. PREPARING AN EA FOR SUBMISSION TO CDER

A. When is an EA or AEA required under the regulations?

Preparation of an environmental assessment is ordinarily required unless the proposed action qualifies for exclusion under 21 CFR §§ 25.23 and 25.24. EA's are submitted to CDER for among other actions: 1) NDA's and 2) efficacy or other supplements to existing NDA's or actions on ANDA's or AADA's, if the approved drug product will be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect, or if data available to the agency establish that at the established levels of exposure, the substance may be toxic to organisms in the environment.

1. NDA's

Type 1 NDA's are for new molecular entities. NDA Types 2-7 are for drug products which have already been marketed or approved in the same form or very similar form in the U.S. **The regulations require that an EA or AEA be provided for all NDA's.**

2. NDA Supplements

Under FDA's NEPA procedures, an EA or AEA must be prepared if the supplemental application does not qualify for a categorical exclusion. If an EA or AEA has previously been submitted for the same active moiety by the applicant, the EA or AEA for the supplement need only include a copy of the original EA/AEA and a discussion of the differences/changes from the original application and the impact of these differences on the environment from those described in the original EA/AEA. For each EA format item that does not differ from the original EA/AEA, this should be stated and a reference to the previously submitted EA provided. If the applicant is abstracting information from an environmental assessment/FONSI released under the Freedom of Information Act (FOIA), a copy of the document should be included with the submission. If no previous EA/AEA can be referenced, an EA or AEA, as appropriate, should be provided in accordance with the content and format information provided in section III.D.

3. ANDA/AADA's

Under FDA's NEPA procedures, an EA or AEA must be prepared if the ANDA/AADA application or supplement to an ANDA/AADA does not qualify for categorical exclusion. If an EA or AEA has previously been submitted for the same active moiety by the applicant, the EA or AEA need only include a copy of the original EA/AEA and a discussion of the differences/changes from the original application and the impact of these differences on the environment from those described in the original EA/AEA. For each EA format item that does not differ from the original EA/AEA, this should be stated and a reference to the previously submitted EA provided. If the applicant is abstracting information from an environmental assessment/FONSI released under the Freedom of Information Act (FOIA), a copy of the document should be included with the submission. If no previous EA/AEA can be referenced, an EA or AEA, as appropriate, should be provided in accordance with the content and format information provided in section III.D.

4. IND's

Under FDA's NEPA procedures, an EA or AEA must be prepared if the action does not qualify for a categorical exclusion.

B. What type of EA should be submitted?

FDA's NEPA procedures provide for two types of EA's: "full" EA's or abbreviated EA's. A "full" EA consists of 15 format items, including characterization of the fate and effects in the environment of the compound which is the subject of the proposed action. AEA's exclude or limit some of the information required including that in EA format items 7 and 8, fate and effects testing. The information to be provided for each of the format items is described in 21 CFR § 25.31a and in section III.D of this document.

FDA believes that, as stated in 21 CFR § 25.1(b), environmental documents are to concentrate on timely and significant issues, not to amass needless detail. FDA 's regulations (21 CFR § 25.31a(b)) provide that for various actions, certain format items of the EA may be abbreviated. For other drug product approvals requiring an EA pursuant to 21 CFR § 25.31a(a), the EA generally should address format items 1-15, but in some cases, not all format items may apply (see section III.D.7 for additional information). If a preparer of an EA believes that not all items in the format apply, the applicant may consult the Environmental Assessment Team at CDER to agree on a different format.

FDA's regulations at 21 CFR §25.31a(b) describe three types of CDER actions which are eligible for an AEA: 1) infrequent uses; 2) naturally occurring substances; and 3) products approved by the Environmental Protection Agency (EPA).

The basis for an AEA should be stated in EA format item 4.a. After CDER evaluates the environmental information submitted in an EA in which one or more EA format items are abbreviated, CDER may require the submission of additional information.

1. Infrequent Use AEA's

The infrequent use provision allows for preparation of an AEA when the drug product is intended for the prevention, treatment, or diagnosis of a rare disease or for a similarly infrequent use; for ophthalmic or topical application; or for local or general anesthesia (21 CFR § 25.31a(b)(3)).

For infrequent use AEA's, documentation for EA format items 7-11 and 15 is ordinarily not required. Questions have arisen regarding the interpretation of rare disease or condition under this provision. CDER is providing guidance regarding this provision as follows: "Rare disease or condition" is defined in the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bb(a)(2) as "any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such a drug." Criterion A may be supported by designation as an Orphan Drug by FDA's Office of Orphan Products Development or by providing the estimated patient population and supporting information from an independent source (*e.g.,* Centers for Disease Control and Prevention (CDC)). If a drug has been designated as an Orphan Drug under criterion B, an infrequent use AEA may be used.

2. Naturally Occurring Substances AEA's

An AEA may be submitted for organic or inorganic drug substances, whether obtained from a natural resource or synthesized, that will exist in the environment in the same form as a substance found naturally in the flora, fauna, atmosphere, water or soil. A modified active moiety (*e.g.,* salt) which does not occur naturally also may be supported by an AEA filed under § 25.31a(b)(5) if it is established that, *in vivo* and in the environment, the active moiety exists in a form that is found naturally.

AEA's for substances that occur naturally in the environment should discuss whether the use of the product can reasonably be expected on the basis of all available evidence to alter significantly the concentration and distribution of the product, its metabolites, degradation products or its constituent parts in the environment (EA format item 7). These AEA's may rely on **existing** data (*i.e.,* from literature or data previously generated by the applicant) to fulfill the reporting requirements of EA format item 8 (effects). If a substance does not occur naturally in the geographic area of proposed drug use and disposal, additional information may be needed.

More information is available in section V regarding drug substances that are obtained from natural resources.

3. AEA's for Products Approved by EPA

AEA's for products that have been approved by the Environmental Protection Agency (EPA) under section 4 or 5 of the Toxic Substances Control Act (TSCA) or under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) should rely on environmental information in studies submitted to EPA, in the application/ petition submitted for FDA approval, and in the scientific literature to fulfill the requirements of EA format items 7, 8 and 15 (21 CFR § 25.31a(b)(6)). The AEA should contain a

description of any potential adverse environmental impact determined by the EPA.

C. What EA information should be provided in an application?

The applicant should determine whether a categorical exclusion, AEA or EA is appropriate for their submission and provide the required information in the initial filing. **Failure to provide: 1) a claim of categorical exclusion with certification of compliance with the categorical exclusion criteria; or 2) an adequate EA or AEA (*e.g.,* information for each required EA format item), is grounds for refusing to file the application (21 CFR §314.101(d)(4) and §25.23(d)).**

If the submission is eligible for more than one type of environmental assessment format (*e.g.,* a naturally occurring substance for a rare disease for which one could prepare an AEA either under 21 CFR § 25.31a(b)(3) or (5)), the applicant should submit the information in the format with the fewest reporting requirements and state which EA format is being used. CDER will request additional information if warranted.

D. Content and Format

This section describes the basic information that should be submitted for each format item in an EA or AEA and follows the formats described in FDA's NEPA procedures (21 CFR § 25.31a). Attachment A contains an outline of the format for an EA.

1. Date

The EA should include the date the EA was originally prepared and the date(s) of any subsequent amendments.

2. Name of Applicant/Petitioner

The EA should identify the applicant who is submitting the application.

3. Address

The EA should contain the address where all correspondence is to be directed.

4. Description of Proposed Action

a. Requested Approval

The description of the requested approval should include the drug product application number (if available), drug product name, dosage form, strength, a brief description of the drug product packaging, whether an EA or AEA is provided and, if applicable, the basis for the AEA. For example, "XYZ Pharmaceuticals has filed an NDA pursuant to

section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME® (established name), 250 mg and 500 mg, packaged in OHDPE bottles. An EA has been submitted pursuant to 21 CFR § 25.31a(a)."

b. Need for Action

The EA should briefly describe the drug's intended uses in the diagnosis, cure, mitigation, treatment or prevention of disease. If attempting to qualify an action for an abbreviated environmental assessment because it is used to treat a rare disease or condition (see section III.B.1), it should be indicated if the drug is for acute or long-term use, the current and/or expected patient population (*i.e.,* total patient population, not marketing estimate) and Orphan Drug status, if applicable.

c. Production Locations

The EA should identify the location of both the drug substance and the drug product manufacturing facilities. The location of production facilities for isolated drug substance intermediates should also be provided if the intermediates are not commercially available to all parties in the open marketplace (*i.e.*, proprietary drug substance intermediates). The EA should include a statement whether any intermediates are considered proprietary. The specific street address(es) should be provided. A brief description of the environments at and adjacent to the facilities should be provided. The zoning (*e.g.*, industrial, commercial, residential) and any geographic features (*e.g.*, mountains, lakes, rivers, forests) in proximity to the manufacturing facilities should be identified.

If primary packaging operations are conducted at locations other than the drug product manufacturing facility, the sites of those operations should be identified.

Information ordinarily need not be provided for secondary packaging operations, labeling, testing, quality control, distribution and warehousing operations which are performed at locations other than the manufacturing facilities, or primary packaging facilities where the introduction of drug substance, proprietary drug substance intermediate or drug product into the environment is minimal (*e.g.*, due to accidental breakage, emission from nondestructive testing). If standard procedures at any of these facilities allow for introduction of other than incidental quantities of these compounds into the environment, then information should also be included for those facilities.

The names and addresses of manufacturers or suppliers that are excluded from public release under FOIA procedures may be treated as confidential information when preparing an environmental assessment and may be included in a confidential appendix (see section III.G for a discussion of confidential and non-confidential

information). All other information regarding these facilities (*e.g.,* EA format item 6) should be included in the non-confidential EA summary document and identified in such a manner to clearly indicate the operation conducted at the facility (*e.g.,* Contract Manufacturer - Drug Substance, Contract Primary Packager #1, Contract Primary Packager #2).

Note that for each facility identified in this section, information should be provided under EA format item 6 unless it is a foreign site with appropriate certification (see section VI).

d. Locations of Use

The EA should identify the location(s) of end use of the drug product. Typically, the locations of use are identified as hospitals, clinics and/or patients in their homes. If use is expected to be concentrated in a particular geographic region, this fact should be included.

e. Disposal Sites

The EA should describe the method(s) of disposal of rejected, expired, returned or waste drug substance, proprietary drug substance intermediate, and drug product. The applicant should provide a brief, general description of the method(s) of disposal including whether the facilities that will be used are permitted by an appropriate authority to destroy hazardous or non-hazardous material. The company/facility currently responsible for disposal should be identified as should: 1) the license or permit number; 2) the EPA or other issuing authority's identification number, if any; 3) the license or permit expiration dates; and 4) the issuing agent. For example, "Returned, expired or rejected drug product will be disposed of by high temperature incineration at a facility which is licensed by the EPA or an appropriate state authority to destroy hazardous materials. The facility currently being used is XYZ Incinerators, 1234 Good Ave., Burn, AK which is licensed by the EPA to destroy hazardous material under permit 1234 (expiration date 12/1999))." **Copies of the actual permits/licenses do not need to be submitted.** A reference to EA format item 6.b, "Controls Exercised," may be provided if the disposal operations are described there. Specific information regarding contract disposal facilities (*e.g.,* identification, licensing information) may be included in a confidential appendix. (See section III.G for a discussion of confidential and non-confidential information).

Unless other disposal methods by the end user are anticipated, it is sufficient to state that at U.S. hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy or clinic procedures and/or that in the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, although minimal quantities of unused drug may be disposed of in the

sewer system.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

The EA should contain information to allow for accurate location of data about the chemical in scientific literature and to allow for identification of closely related compounds. At a minimum, the information listed below should be provided. Other information, such as the International Nonproprietary Name (INN) or nonsystematic/ semisystematic chemical names, should be included if deemed useful in the identification of the compounds.

Usually this information need only be provided for the drug substance, but the same information should also be provided for the form of the active ingredient in the drug product if it is different from the drug substance (*e.g.*, a salt formed *in situ* from a free base) or for a pharmacologically active related substance formed by conversion from a pharmacologically inactive parent compound (*e.g.*, a prodrug product is converted to the pharmacologically active form). Although the following information is generally self-explanatory, explanation is provided, where appropriate:

a. Nomenclature

i. Established Name (U.S. Adopted Name-USAN)

ii. Brand/Proprietary Name

iii. Chemical Names

(1) Chemical Abstracts (CA) Index Name (inverted form)

(2) Systematic Chemical Name (uninverted form)

b. Chemical Abstracts Service (CAS) registration number

c. Molecular Formula

d. Molecular Weight

e. Structural (graphic) Formula

f. Physical Description

For example, white to off-white powder

g. Additives

The EA should identify by name and CAS registration number any substance added to the described chemical substance in relatively small amounts to impart or improve desirable properties or suppress undesirable properties (*e.g.,* formulation excipients, preservatives) which is expected to be emitted into the environment. A reference to EA format item 6.a is acceptable as long as the additives are included in the list of "Substances Expected to be Emitted."

h. Impurities

Impurities in drug substances and products are controlled and are typically found at very low levels (*i.e.,* much less than 1%). The EA should only identify impurities likely to be found in the described chemical substance at levels > than 1%. CAS registration numbers should be provided, if available. Reference in the EA document to a confidential appendix which provides this information is adequate. Identification in this section of the EA of potential residual solvents is not necessary if solvents are adequately addressed in EA format item 6.a.

6. Introduction of Substances into the Environment

Information should be provided in EA format items 6.a through 6.e for all facilities identified in EA format item 4.c, unless a facility is a foreign facility with appropriate certification (see section VI). The information should be presented separately for each facility. The extent/detail of information necessary for primary packaging operations depends on the dosage form and the potential for introduction of chemical substances into the environment.

The obligation for a company to obtain the proper emission permits and comply with all applicable Federal, State and local emission requirements is not negated by FDA review of an environmental assessment or approval of an application.

a. Substances Expected to be Emitted

The substances expected to be emitted from the facilities should be listed. Substances that are emitted at low levels need not be listed unless they are likely to have a significant environmental impact. The list(s) should include the CAS registration number for each and the manner in which they are expected to be emitted (*e.g.*, organic solvent waste stream). Reference in the EA document to a confidential appendix which provides this information is adequate.

b. Controls Exercised

The EA should contain a brief description of the controls associated with the air, liquid, and solid emission waste streams identified in EA format item 6.a. Descriptions of control efficiencies (*e.g.*, emission of airborne particulate material is controlled by HEPA filtration with a 99.9% operating efficiency) or treatment prior to emission (*e.g.*, neutralization of aqueous waste streams) should be included, if applicable. Disposition of unused product or rejected packaged goods, including those at contract packagers, should be discussed in EA format item 6.b if it has not been described in EA format item 4.e. Disposal of manufacturing aids, emission controls or other items (*e.g.*, resins, filters, clothing) which may contain residual drug substance or proprietary drug substance intermediates should be discussed.

c. Citation of and Statement of Compliance with Applicable Emission Requirements

A citation (*i.e.*, list of regulations/laws) of all applicable Federal, State and local emission requirements, including occupational, should be provided, as well as a statement of compliance with, or being on an enforceable schedule to be in

compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the manufacturing operations.

Material safety data sheets (MSDS) should be provided in a non-confidential appendix for the drug substance and if appropriate, drug product.

A list of emission permits and/or licenses should be provided along with the number, authorizing agency and expiration dates. **Inclusion of the actual permit and/or license is not necessary.** Any of the requested information that is not applicable or not current for a specific permit/license (*e.g.*, expired permit) should be explained. If no permits are required, this should be stated (e.g., air emissions are below the level that requires a permit). For ease of review, CDER prefers that this information be presented in a table format (see Attachment B for a sample table).

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

The EA should state whether approval and the subsequent increase in production at the facility is expected to affect compliance with current emission requirements and should contain a brief supporting discussion based on the estimated fifth year production volume (*e.g.*, waste water emission will increase to approximately 60% of the permit limit).

e. Expected Introduction Concentrations

For the drug substance and/or active moiety entering the environment as a result of use and disposal, expected introduction concentrations for use and disposal should be estimated, either through use of calculations or direct measures. The estimates for use should be based on total fifth year production estimates for all dosage forms and strengths included in the application or related (companion) applications. All concentrations should be reported as the concentration of active moiety rather than, for example, the salt or complex. The specific calculations and the basis for the calculations (*e.g.,* 5th year production estimates) may be included in a confidential appendix.

Based on the identification of and literature about emitted substances other than the drug substance/active moiety, CDER can determine whether it needs more information about the potential environmental impacts of these other emissions (see EA format item 6.a). Such additional information generally will not be needed.

Note: for substances occurring naturally in the environment, calculations may aid in preparing the discussion of the concentration and distribution of the substance in the environment which is called for in EA format item 7 (21 CFR § 25.31a(b)(5)) .

i. Expected Introduction Concentration from Use

The calculation of the expected introduction concentration (EIC) entering into the aquatic environment from patient use may include consideration of metabolism to less pharmacologically active or inactive compounds and the environmental depletion mechanisms that occur in the waste treatment process (*e.g.,* adsorption, degradation, hydrolysis), if the information is available. Information should be provided regarding the metabolic profile and pharmacological activity of the metabolites relative to the active moiety if metabolism is considered.

The EIC for the aquatic environment, assuming all drug substance produced is used, even distribution throughout the U.S. per day, and no metabolism or depletion mechanisms, should be calculated as follows:

EIC-Aquatic (ppm) = A x B x C x D

where A = kg/year production
B = 1/liters per day entering POTW's*
C = year/365 days
D = 10^6 mg/kg (conversion factor)

* 1.115 x 10^{11} liters per day entering publicly owned treatment works (POTW's), Source: 1992 Needs Survey, Report to Congress, September 1993, EPA 832-R-93-002

This equation should be used when determining if the Tier 0 approach will be used unless localized use is expected (see section III.D.7.c). If an alternative calculation is used in addition to the equation provided above, it should be clearly indicated in the EA and the source and/or basis for the alternative calculation provided. An alternative calculation should be used if localized use of the drug product is expected.

Some drug substance and/or active moiety may enter the terrestrial environment when sludge from waste water treatment facilities, which contains adsorbed material, is applied to land. Although application of sludge to land is regulated by EPA or an appropriate State authority, controls similar to those at landfills are not in place to limit the release of materials in the environment after application. Sludge is generally subjected to some form of aerobic or anaerobic digestion in the waste treatment facility, and only a fraction of the sludge may be applied to soil while the remainder is incinerated or landfilled. The EIC for the terrestrial compartment should be estimated if, based on the available physical/chemical properties of the compound, significant

quantities of the active moiety are expected to adsorb to sludge and typical POTW procedures allow for significant quantities of sludge to be disposed of in this manner. The calculations used depend on the treatment/disposal process. Depletion mechanisms (*e.g.,* biodegradation, hydrolysis) that occur in the waste treatment process may be considered when calculating the EIC for the terrestrial compartment, if the information is available.

The concentration expected in the atmospheric compartment should be considered for products that are released primarily into the air (*e.g.,* medical gases).

ii. Expected Introduction Concentration from Disposal

Normally, the EIC from disposal need not be calculated since the majority of pharmaceutical waste will be disposed of in landfills or at incineration facilities which are regulated by the EPA or appropriate State agencies. These agencies have considered the environmental impacts from the operation of these facilities in their licensing process and require controls (*e.g.,* scrubbers, lined landfills, migration tests) to limit the release of materials into the environment. The EIC for disposal should be calculated if significant quantities of material (*e.g.,* rejected batches) are expected to be disposed of in the sewer system.

7. Fate of Emitted Substances in the Environment

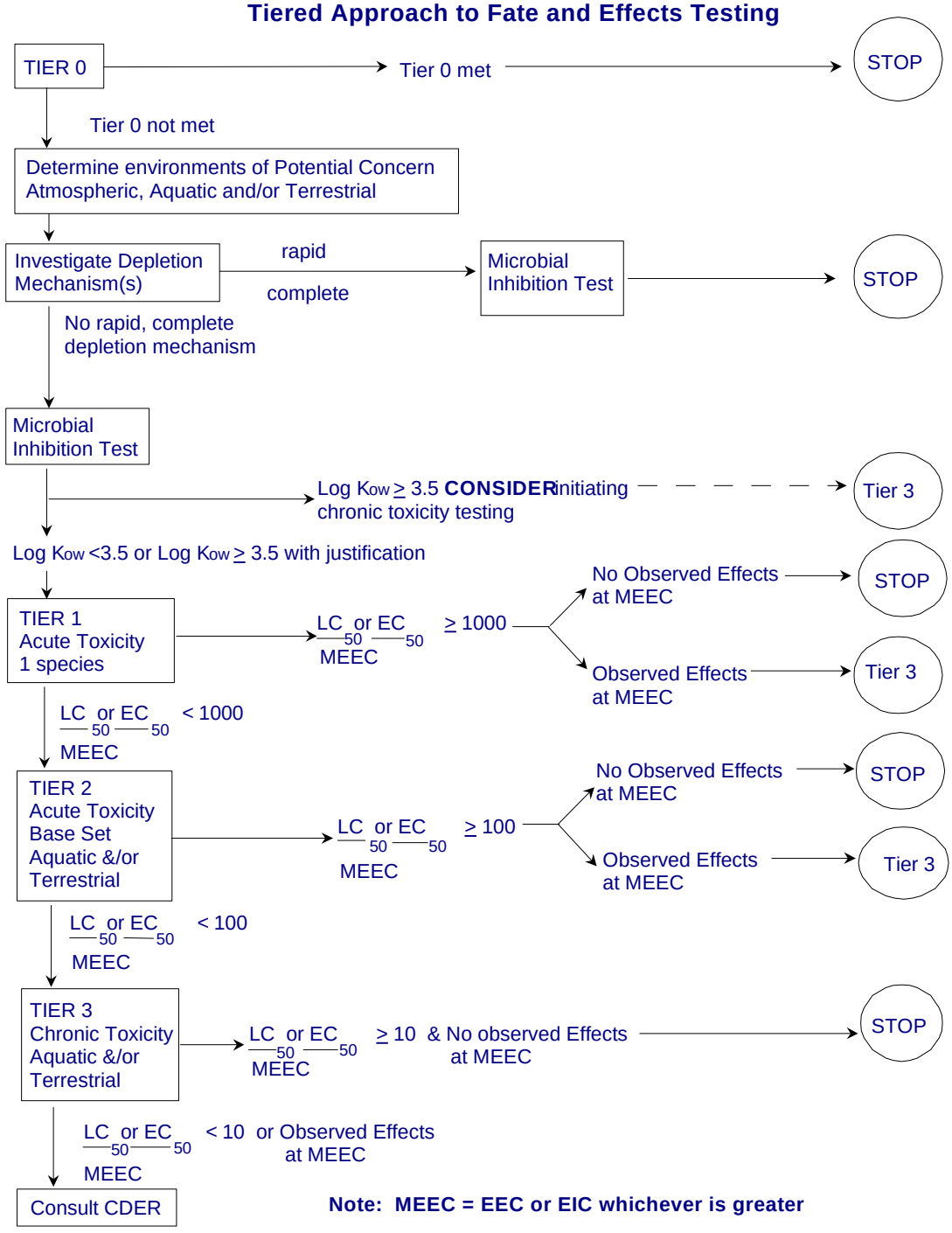
a. Tiered Approach to Determining Environmental Fate (EA format item 7) and Effects (EA format item 8)

The Center encourages the use of a logical, tiered approach to testing so that adequate information is available to assess the potential environmental fate (EA format item 7) and effects (EA format item 8) of pharmaceuticals while minimizing the cost to industry. Information is provided in EA format item 7.c (Tier 0) and EA format item 8 (Tiers 1-3) regarding an acceptable approach to tier testing. Figure 1 provides an illustration of this tiered approach. Alternative, scientifically justified approaches may also be used.

If EA format items 7 and 8 are needed, the information provided should focus on the fate and effect of the drug substance and/or structurally related substances (SRS's) rather than, for example, excipients, solvents or raw materials used in producing the drug substance, proprietary drug substance intermediate, or drug product. Based on the identification of and literature about emitted substance

other than the drug substance or SRS's, CDER can determine whether it needs more information about the potential environmental impacts of these other emissions. Such additional information generally will not be needed.

Figure 1
Tiered Approach to Fate and Effects Testing



Information submitted under EA format items 7 and 8 may include specific data generated on the test substance or relevant information on analogous compounds from the submitter or from the peer reviewed literature as appropriate. Actual experimental data regarding base parameters are generally preferable to computer modeling; however, in some circumstances computer modeling may be appropriate. FDA may be consulted if a company believes computer modeling is appropriate and wishes to use modeling in an EA.

b. Type of Fate Information to be Submitted

i. EA's filed pursuant to 21 CFR § 25.31a(a)

Information listed in section III.D.7.d may not be needed if an applicant follows a tiered approach to preparing an environmental assessment (see Tier 0 approach described in section III.D.7.c).

ii. EA's filed pursuant to 21 CFR § 25.31a(b)(3)

Fate information normally need not be submitted in AEA's for drugs intended for the prevention, treatment, or diagnosis of a rare disease or for a similarly infrequent use; for ophthalmic or topical application; or for local or general anesthesia (21 CFR § 25.31a(b)(3)).

iii. EA's filed pursuant to 21 CFR § 25.31a(b)(5)

AEA's for substances that occur naturally in the environment should contain a discussion of whether, on the basis of all available evidence, the use of the product can reasonably be expected to alter significantly the concentration and distribution of the product, its metabolites, degradation products, or its constituent parts in the environment (21 CFR § 25.31a(b)(5)). The natural source of the substance (*e.g.*, endogenous to all mammalian cells), and the production volume relative to the estimated quantity occurring naturally in the environment, if known, should be provided. Information in section III.D.7.d may not be needed if an applicant follows a tiered approach to preparing an environmental assessment (see Tier 0 approach described in section III.D.7.c).

iv. EA's filed pursuant to 21 CFR § 25.31a(b)(6)

AEA's for products that have been approved by the Environmental Protection Agency (EPA) under section 4 or 5 of the TSCA or under FIFRA should rely on environmental information in studies submitted to EPA, in the application/ petition submitted for FDA approval and in the scientific literature (21 CFR § 25.31a(b)(6)).

c. Tier 0

CDER has performed a retrospective review of toxicity information available in EA's previously submitted in support of NDA's and NDA supplements. Data are available from each reviewing division and are representative of pharmacological drug classifications. The data have routinely shown no observed effects on relevant standard environmental test organisms at drug concentrations below 1 part per billion (ppb). Because CDER has routinely found that drugs at concentrations less than 1 ppb have no significant effect on relevant standard test organisms, and, therefore, are unlikely to have a significant effect on the environment, CDER has determined that information for EA format items 7, 8, 9, 10, 11 and 15 will normally not be needed for drugs whose maximum expected environmental concentration (EEC or EIC whichever is greater) is less than 1 part per billion.

EA format items 7, 8, 9, 10, 11 and 15 will normally not be needed when the expected environmental concentration due to entry into the environment is less than one (1) ppb from use and/or disposal or at any point where higher concentrations are expected as a result of bioaccumulation or other types of concentration processes. Additionally, for those actions involving genetically modified organisms and cells, the applicant should be using a containment class for manufacturing established by a recognized authority (*e.g.,* National Institutes of Health's Recombinant DNA Advisory Committee) or consideration of the fate and effects of the use of the modified organisms or cells should be included as an integral part of the CDER application review process (*e.g.,* manufacturing process validation) if the Tier 0 approach is used to limit the information submitted in EA format items 7, 8, 9, 10, 11 and 15.

Under specific circumstances, such as those identified in section II as reasons for denying a categorical exclusion, EA format items 7, 8, 9, 10, 11 and 15 may have to be submitted even if the Tier 0 approach is used. CDER encourages consultation if there are any questions regarding the applicability of Tier 0 to a particular drug product.

See EA format items 6.e and 7.d.iv for information regarding concentration calculations.

d. Fate information to be submitted for an EA filed pursuant to 21 CFR § 25.31a(a)

If the Tier 0 approach (see section III.D.7.c) cannot be used by an applicant, the following information should be provided.

i. Identification of Substances of Interest

The actual substances which will enter or exist in the environment (*i.e.,* atmospheric, aquatic, terrestrial) may include the parent compound (*i.e.*, drug substance) or SRS's such as the dissociated parent compound, metabolites or degradants. The EA should list the drug substance and the **predominant** SRS's expected to enter or exist in the environment, provide the name, chemical structure and CAS number when possible, and provide a rationale for the decision as to which substance(s) will be studied. Predominant SRS's should be considered those greater than 10% of dose.

In most cases, fate (and effects) information should be provided on the parent (or active) drug substance, as representative of substances entering the environment. Such information is relevant to SRS's when these possess the same fundamental structure and are comparably or more polar than the parent drug substance. At a minimum, the EA should contain a discussion of the potential fate and effects of the predominant SRS's based on their structural differences/similarities to the parent compound *(e.g.*, due to a functional group change, the metabolite should be more soluble than the parent compound, the SRS is more polar). Computerized structure/activity relationship modeling programs may be useful in supporting extrapolation of fate and effects information from the parent (or active) drug substance to the SRS. Relevant available pharmacologic activity and toxicity information should be provided for the SRS's. Specific toxicity/activity information for SRS's may be included in a confidential appendix. Additional environmental information on a predominant SRS may be warranted, following consultation with the Environmental Assessment Team at CDER, if the fate of the compound is expected to differ from the parent compound or there is an indication that the SRS's effect on the environment would be substantially greater than from the parent drug substance.

ii. Physical/Chemical Characterization

The following tests should be conducted to determine if the compound is most likely to amass predominantly in aquatic, terrestrial and/or atmospheric environments:

(a) Water Solubility

(b) Dissociation Constant(s)

(c) Octanol/Water Partition Coefficient

(d) Vapor Pressure or Henry's Law Constant

If there is a scientific basis for not performing a test, the justification should be included in the EA (*e.g.*, water solubility was not determined because the compound is hydrolytically unstable). For a test compound that associates or dissociates in water, water solubility and the octanol/water partition coefficient may have to be determined at pH 5 and 9 as well as pH 7.

The octanol/water partition coefficient (K_{ow}) is an indicator of a nonionized compound's potential to adsorb to the organic fraction of soil, sediment or sludge in addition to being an indicator of a compound's lipophilicity. It is not as good a predictor for inorganic chemicals, metal organic complexes, dissociating, ionic organic compounds or compounds with other mitigating structural features such as molecular size. Further study of the sorption/desorption properties (K_{oc}) of a substance to sludge should be **considered** if log K_{ow} is greater than 3 or other properties indicate that sorption/desorption may occur.

iii. Environmental Depletion Mechanisms

Depletion mechanisms should be investigated to determine if there is degradation of the compound in the environment(s) of interest. **It is not necessary to go to extraordinary effort to identify a depletion mechanism once the typical depletion mechanisms (i.e., hydrolysis, photolysis, biodegradation) have been investigated nor to continue investigating all potential depletion mechanisms once one has been identified.** Consideration should be given to the nature and extent of the degradation. If a rapid, complete depletion mechanism is identified (degradants are relatively simple, polar by-products), no testing to determine the environmental effects of the compound should be performed except for a microbial inhibition test or other appropriate test to assess the potential for the compound to disrupt waste treatment processes. Based on the estimated time prior to emission from a treatment facility, CDER considers the following to be rapid depletion mechanisms:

Hydrolysis $t_{½}$ (pH 5-9):	$\leq$ 24 hours
Aerobic Biodegradation $t_{½}$:	$\leq$ 8 hours
Soil Biodegradation $t_{½}$:	$\leq$ 5 days

It is usually sufficient to provide basic supporting information that identifies the potential for a compound to be removed from the environment by a depletion mechanism (*e.g.,* photolysis or hydrolysis based on information developed for analytical methods validation or from stability studies). If the depletion mechanism is being used to reduce the expected introduction concentration (EA format item 6.e) or to eliminate effects testing, a formal, detailed analysis of the depletion mechanism should be provided (*e.g.,* according to a standard test method, rate determination, analysis of expected exposure time in the environment).

Direct and indirect photolysis, although significant under laboratory conditions, may not be a rapid depletion mechanism in the environment due to significant variation in light intensity (*e.g.*, related to weather, latitude, depth penetration) and duration of exposure. Efforts to characterize photolysis as a depletion mechanism should take these factors into consideration.

iv. Expected Environmental Concentration (EEC)

The expected environmental concentration is the expected concentration of the active moiety or other compound of interest (see EA format item 7.d.i) that organisms would be exposed to in the environment (*e.g.,* surface water) after consideration of, for example, spatial or temporal concentration or depletion factors such as dilution, degradation, sorption and/or bioaccumulation. A brief discussion comparing the EEC to the EIC (see EA format item 6.e) should be provided. In the majority of cases the EEC would be expected to be significantly less than the EIC due to dilution in the aquatic environment.

v. Summary

A summary discussion of the environmental fate of the substance(s) of interest should be provided for the following environmental compartments based on the information and data provided in EA format items 7.d.i-iv. In some circumstances, transport between environmental compartments should be considered when determining the fate of the substance(s) of interest in the environment.

Aquatic Environment: In general, pharmaceutical substances are expected to enter predominantly into the aquatic environment and, therefore, the focus of any effects studies will most likely be on aquatic organisms. If the substance(s) of interest rapidly degrades (see EA format item 7.d.iii) or adsorbs completely and irreversibly to sludge, then fate and effects in the aquatic environment should not usually be considered.

Terrestrial Environment: In general, substances enter the terrestrial environment predominantly from sludge removed from waste water treatment plants that is subsequently applied to land (see EA format item 6.e.i). Therefore, effects on the

terrestrial environment are more likely if a compound adsorbs to sludge. Sludge is generally subjected to some form of aerobic or anaerobic digestion in the waste treatment facility and only a fraction of the sludge may be applied to soil while the remainder is incinerated or landfilled. Fate and effects testing in the terrestrial environment should be **considered** if testing indicates that the substance(s) of interest will significantly adsorb to sludge (*e.g.*, $K_{oc} \geq 1000$) and if based on typical POTW processes, a significant quantity of sludge is expected to be applied to land.

Atmospheric Environment: In general, substances that do not adsorb readily to soils, have a high vapor pressure and have a low water solubility are likely to volatilize significantly from the aquatic or terrestrial environments, although actual volatilization rates will depend on environmental conditions (*e.g.*, dispersion away from the evaporation site) and on factors that can lessen or enhance the effective vapor pressure or behavior of the chemical at a liquid-air or solid-air interface. The atmospheric compartment may be of interest for medical gases. But based on the polarity of the majority of compounds at relevant aquatic environmental conditions, it is unlikely that there would be substantive partitioning from the aquatic to the atmospheric environment for other pharmaceuticals. Any potential for a substance to volatilize and recycle into the aquatic or terrestrial environments should be discussed based on the information and data available for the substance.

8. Environmental Effects of Released Substances

EA's filed pursuant to 21 CFR § 25.31a(a): Information in EA format item 8 may not be needed if an applicant follows a tiered approach to preparing an environmental assessment (see Tier 0 approach described in section III.D.7.c). Guidance is provided below regarding the tiered approach to effects testing, when testing is indicated.

EA's filed pursuant to 21 CFR § 25.31a(b)(3): Effects information normally need not be submitted for AEA's for drugs intended for the prevention, treatment, or diagnosis of a rare disease or for a similarly infrequent use, for ophthalmic or topical application, or for local or general anesthesia (21 CFR § 25.31a(b)(3)).

EA's filed pursuant to 21 CFR § 25.31a(b)(5): AEA's for substances that occur naturally in the environment should report **existing** data relating to the environmental effects of substances expected to be emitted into the environment as a consequence of use of the product and report information obtained from the scientific literature on the toxicity of the product to laboratory animals, *e.g.*, that information used to satisfy human safety requirements, and to organisms in the environment, *e.g.*, fish invertebrates, plants, fungi, and bacteria, that may be exposed to the product. Information in EA format item 8 may not be needed if an applicant follows a tiered approach to preparing an environmental assessment (see Tier 0 approach described in section III.D.7.c).

EA's filed pursuant to 21 CFR § 25.31a(b)(6): AEA's for products that have been approved by the Environmental Protection Agency (EPA) under section 4 or 5 of TSCA or under FIFRA should rely on environmental information in studies submitted to EPA, in the application/petition submitted for FDA approval and in the scientific literature (21 CFR § 25.31a(b)(6)). The EA should contain a description of any potential adverse environmental impact determined by the EPA.

Tiered approach to environmental effects testing (see below, Microbiological Inhibition Testing through Tier 3 Testing): If effects data are needed and no rapid, complete depletion mechanism has been identified, it should be assumed that the compound will persist in the environment for some time and, therefore, the toxicity of the released substances to environmental organisms should be evaluated. The fate of the substance as determined in EA format item 7 should be considered when designing the studies. For those compounds which enter the atmospheric environment, testing should be designed based on the extent to which the substance recycles into the aquatic or terrestrial environments. All toxicity test results for the drug substance should be reported in terms of the quantity/concentration of the active moiety. The results of the toxicity testing should be compared to the maximum expected environmental concentration (MEEC: EIC or EEC whichever is greater) and the difference between the values discussed (*e.g.,* in terms of the assessment factor, > 1000, > 100). When using this tiered approach to effects testing, it is important to design the test conditions appropriately so that a no observed effects concentration is determined.

Microbial Inhibition Testing: A microbial inhibition test or other appropriate test (*e.g.*, respiration inhibition testing) should be performed to assess a chemical compound's potential to inhibit microorganisms and subsequently disrupt waste treatment processes.

Assessment Factors: These assessment factors are intended to provide a consistent regulatory basis for determining when additional ecotoxicity testing should be performed (tiered approach). They are directly related to the amount of valid ecotoxicity data available. If the LC_{50} or EC_{50} or other appropriate test endpoint divided by the MEEC is less than the assessment factor, additional testing should be performed. The use of EC_{50} or test end point other than the LC_{50} should be limited to those test organisms for which the LC_{50} is not the test endpoint.

TEST TIER	ASSESSMENT FACTOR
1	1000 (see below)
2	100 (see below)

3	10 (see below)

Alternative scientifically justified approaches may also be used.

Tier 1 Testing: Acute ecotoxicity testing should be performed on a minimum of one suitable test organism (see base set for Tier 2 Testing). If the EC_{50} or LC_{50} divided by the MEEC is greater than 1000, no further testing should be conducted unless sublethal effects are observed at the MEEC. If the EC_{50} or LC_{50} divided by the MEEC is less than 1000, Tier 2 testing should be performed. Sublethal effects (observed effects) at the MEEC indicate that chronic toxicity testing (Tier 3) should be performed. The use of the assessment factor of 100 could be used for Tier 1 Testing if there is evidence (*e.g.,* Tier 2 Testing on a similar compound) to support that the single test organism used would be expected to be the most sensitive of the base set test organisms.

Tier 2 Testing: Acute ecotoxicity testing should be performed on the minimum base set of aquatic and/or terrestrial organisms. The aquatic base set usually consists of: 1) a fish acute toxicity test; 2) an aquatic invertebrate acute toxicity test; and 3) an algal species bioassay. The terrestrial base set usually consists of: 1) plant early growth tests; 2) earthworm toxicity test; and 3) soil microbial toxicity test. Usually only an earthworm toxicity study is indicated if the substance binds tightly to soil. A rodent acute toxicity is not included in the terrestrial base set since there is usually a significant quantity of mammalian (*e.g.,* mice, rat, dog, monkey, humans) toxicity testing performed, both acute and chronic, to support the underlying application and to demonstrate the safety of the drug product. **Consultation with the Environmental Assessment Team at CDER is suggested prior to initiating any terrestrial studies.** If the EC_{50} or LC_{50} for the most sensitive organism in the base set divided by the MEEC is greater than 100, no further testing should be conducted unless sublethal effects are observed at the MEEC. If the EC_{50} or LC_{50} divided by the MEEC is less than 100, Tier 3 testing should be performed. Sublethal effects (observed effects) at the MEEC indicate that chronic toxicity testing (Tier 3) should be performed.

Tier 3 Testing: Chronic toxicity testing should be considered if the compound has the potential to bioaccumulate or bioconcentrate, if indicated based on Tier 1 and/or Tier 2 Testing, or if there are other indications that the compound undergoes biotransformation to more toxic compounds.

Bioaccumulation or bioconcentration is a complex, dynamic process which is dependant on the availability, persistence and physical/chemical properties of a compound in the environment. In general, pharmaceuticals tend not to be very lipophilic and are produced/used in relatively low quantities compared to industrial chemicals. The majority of pharmaceuticals are metabolized to some extent in humans to SRS's that are more polar, less toxic and less pharmacologically active than the parent

compound. These factors suggest that there should be a low potential for bioaccumulation or bioconcentration of pharmaceuticals, but because of the length of time it takes to conduct chronic toxicity studies, applicants are encouraged to identify compounds which are candidates for these studies as early as possible. A primary determinant of the potential for a compound to bioaccumulate is the octanol/water partition coefficient (K_{ow}). A high octanol/water partition coefficient indicates that the compound will tend to be lipophilic. Chronic toxicity testing should be **considered** if log K_{ow} of a compound is greater than or equal to 3.5 under relevant environmental conditions (*e.g.,* pH 7), and a justification should be provided if chronic toxicity testing is not performed. Structural features (*e.g.,* molecular size, polarity) that limit passage across biological membranes or the lack of bioavailability to environmental organisms (*e.g.,* strong adsorption to soil) are mitigating factors which could be considered when determining if bioaccumulation/bioconcentration would be a concern for compounds with a K_{ow} greater than or equal to 3.5. It may be necessary to obtain acute toxicity data for the organism to be tested in order to set the concentrations for the chronic studies properly. **If the preparer of an EA is considering initiating chronic toxicity studies, consultation with the Environmental Assessment Team at CDER is recommended to ensure that such studies are appropriate and properly designed.**

For chronic toxicity testing, If the EC_{50} or LC_{50} divided by the MEEC is greater than 10, no further testing should be conducted unless sublethal effects are observed at the MEEC. CDER should be consulted if the EC_{50} or LC_{50} divided by the MEEC is less than 10 or there are sublethal effects at the MEEC.

Test Methods/Test Organisms: Studies should be performed using test organisms and methods which have been identified by the FDA EA Technical Assistance Handbook, the EPA (40 CFR § 797), the Organisation for Economic Co-operation and Development (OECD) or other peer reviewed literature as appropriate for use in environmental studies. If the drug product is intended to act upon an environmental organism (*e.g.*, antiparasitic, antibiotic), information regarding the toxicity to the target organism(s) should be included.

9. Use of Resources and Energy

a. Natural Resources and Energy

The EA should provide the approximate energy usage associated with the manufacturing operations as a percent of the total plant consumption, or other appropriate evaluations. If the drug substance, proprietary drug substance intermediates, or precursors are derived from a natural resource (*e.g.*, plants), the source should be identified, and other pertinent information provided, if applicable, such as geographic region of source, whether the resource is cultivated or harvested from the wild and/or relevant permits (See section V).

b. Effect on Endangered or Threatened Species

The EA should state whether approval is expected to affect, directly or indirectly, endangered or threatened species. If the drug substance, proprietary drug substance intermediates or precursors are derived from a natural resource, the EA should specifically state whether the natural resource is listed as endangered or threatened under the U.S. Endangered Species Act (ESA) or the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES). Endangered or threatened species in the immediate vicinity of any of the production facilities should be identified.

c. Effect on Property Listed in or Eligible for Listing in the National Register of Historic Places

The EA should state whether approval is expected to affect properties listed in or eligible for listing in the United States' National Register of Historic Places. Historic properties in the immediate vicinity of any of the U.S. production facilities should be identified.

10. Mitigation Measures

The EA should contain a summary of measures used routinely in production to mitigate the release of materials into the environment (*e.g.*, compliance with Federal, State and local environmental laws, spill prevention plans). If applicable, a brief description of special measures used to mitigate the release of toxic or potentially toxic materials into the environment should be provided (*e.g.*, special handling information in the product labeling, Occupational Safety and Health Administration (OSHA) requirements, incineration, containment procedures). If there is a discussion of any of these mitigation measures in another section of the

EA, reference to that information is adequate. **Actual copies of mitigation measures *e.g.*, standard operating procedures (SOP's), plans, corporate policies should not be included in the EA.**

11. Alternatives to the Proposed Action

If no potential adverse environmental impacts have been identified for the proposed action, the EA should so state. If potential adverse environmental impacts have been identified for the proposed action, the EA should contain a detailed description of the environmental impact of all reasonable alternatives to the proposed action (including no action, and including measures that FDA or another government agency could undertake as well as those the applicant/petitioner would undertake). The EA should include a description of those alternatives that will enhance the quality of the environment and avoid some or all of the adverse environmental impacts of the proposed action. The environmental benefits and risks of the proposed action and the environmental benefits and risks of each alternative should be discussed.

12. List of Preparers

The EA should include the name, job title, and qualifications (*e.g.,* educational degrees) of those persons preparing the assessment, and should identify any persons or agencies consulted. Contract testing laboratories should be included in the list of consultants, although this may be included in a confidential appendix. ***Curriculum vitae* may be included in lieu of a description of an individual's qualifications, but are not necessary.**

13. Certification

A dated certification should be signed by the responsible official, include the official's title. The following language is recommended:

> "The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of the firm or agency responsible for preparation of the EA.
>
> The undersigned official certifies that the EA summary document (pages x-x) and Appendices x-x (pages x-x) contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR § 1506.6."

The applicant is responsible for the contents of the EA and for signing the certification, whether or not a consultant was used to prepare the EA. The certification should not predate the EA.

14. References

The EA should include a list of citations for all referenced material and standard test methods used in generating data in support of the EA. Copies of referenced articles not generally available which are used to support specific claims in the EA document should be attached in a non-confidential appendix.

15. Appendices

Both confidential and non-confidential appendices may be included (see section III.G for additional information about treatment of confidential information). A list of the appendices should be included in the EA summary document with a designation of confidential or non-confidential following each of the listings. Typically, the non-confidential appendices include Material Safety Data Sheet(s), certification and compliance statements, data summary tables, and copies of referenced articles that are not generally available or which were used in support of specific claims in the EA. Proprietary/confidential information such as emissions or identification of contract facilities and test reports should be included in the confidential appendices.

E. Data Summary Table

To facilitate review, the EA should include a data summary table in a non-confidential appendix (EA format item 15). Attachment C provides an example of a suitable data summary table. Results should not be needed for all items listed if a tiered approach to determining the environmental fate and effects of compounds is used. The table should be modified as appropriate.

F. Test Methods and Report Formats

Test methods and report formats are provided in the FDA EA Technical Assistance Handbook. Equivalent tests, such as those provided by the EPA (40 CFR §§ 796 and 797), the Organisation for Economic Co-operation and Development (OECD) or other validated, peer reviewed methods may be used. The expected minimum level of test performance and test reporting for studies performed to fulfill the requirements of EA format item 7 (fate) is the standards of good scientific practice. The reports submitted in support of fate testing (EA format item 7) should include a description of the test method sufficient for a reviewer to determine the scientific merit of the methodology. The expected minimum level of test performance and test reporting for studies performed to fulfill the requirements of EA format item 8 (effects) is the standards of

FDA's Good Laboratory Practice (GLP) regulations. Guidance on test reporting formats is included in the FDA EA Technical Assistance Handbook or 40 CFR §§ 796 and 797. **Raw test data (*e.g.*, copies of notebook pages, HPLC chromatograms for each assay) should not be included in the EA.**

G. Confidential/Non-Confidential Information

Some of the information that is submitted in an EA is available elsewhere in an application or in a publicly available document. This information may be cross-referenced in the EA, if the information is publicly available. However, the EA should be a stand-alone document, summarizing information that is available elsewhere. The EA will be made public by the FDA as required by regulations issued by the Council on Environmental Quality. Therefore, the EA should contain three distinct parts: 1) the EA summary document which is non-confidential; 2) non-confidential appendices; and 3) appendices with confidential information used to support the EA. All confidential appendices should be at the end of the environmental assessment document. References to non-confidential and confidential appendices may be included in the EA summary document, as appropriate. Confidential data and information which are pertinent to the environmental review of a proposed action and which are submitted in confidential appendices should be summarized in the EA summary document to the extent possible. The EA summary document, non-confidential appendices and FONSI are normally made available for public inspection.

Attachment D provides general guidance as to which information may be included in confidential appendices of the EA. It is the applicant's responsibility to clearly identify the information in the EA which it believes is confidential.

IV. EA'S INVOLVING BIOTECHNOLOGY PRODUCTS

Actions for drugs derived from biotechnology products raise specific concerns regarding the release into the environment of genetically modified microorganisms and cells (*e.g.,* rDNA, bacteria, yeast and plant and animal cells), and fermentation and tissue culture waste media. The EA should: 1) clearly identify that the action involves the use of such materials (EA format item 4.a); 2) describe the biological production system including the host microorganism or cell line and genetic construct(s) (EA format item 5); 3) where appropriate, describe the physical containment and procedures used to prevent release of these materials to the environment as well as relate the containment level to that recommended in the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant

DNA Molecules (*e.g.,* 59 FR 34496, 59 FR 40170, 60 FR 20726) which provides guidance for both research and large scale (Good Large Scale Practices-GLSP) use of organisms containing recombinant DNA molecules (EA format item 6.b);
4) include a description and validation report of the process used to inactivate these materials prior to their release into the environment (EA format item 6.b); 5) discuss the mitigation measures to be taken if the production organism becomes contaminated with other biological agents (*e.g.,* virus, prions, mycoplasma, bacteria, fungi) during production (EA format item 10); and 6) discuss the environmental fate and effect of both the active and inactivated materials if they are to be released into the environment (EA format items 7 and 8).

The discussion for actions involving genetically modified microorganisms and cells should focus on their survivability and colonization potential in the environment and their ability to transfer some or all parts of their genetic material to indigenous organisms. If live microorganisms or cells may be released post-activation or as a result of accidental release during production, studies should be performed to adequately characterize these attributes. The fate of other potentially harmful components (*e.g.,* bacterial toxins) from the genetically modified microorganisms or cells after their release into the environment should be addressed.

V. EA'S INVOLVING DRUGS DERIVED FROM NATURAL RESOURCES

Under the U.S. Endangered Species Act (ESA), Congress declared, "the United States has pledged itself as a sovereign state in the international community to conserve to the extent practicable the various species of fish or wildlife and plants facing extinction, pursuant to the Convention on International Trade in Endangered Species of Wild Fauna and Flora" [CITES] (16 U.S.C. § 1531(a)(4)(F)). Identification as an endangered or threatened species does not preclude the use of material but may necessitate submission of additional information. Under the ESA, if a species has been determined to be endangered or threatened, a federal agency is required to consult with the Secretary of Interior or Commerce to ensure that the agency's actions are not likely to jeopardize the continued existence of threatened or endangered species or their critical habitats (16 U.S.C. § 1536).

When a drug substance, drug substance intermediate, or precursor is derived from a natural resource, the source should be identified. Pertinent information, such as geographic region of source or whether the resource is cultivated or harvested from the wild, should be provided in EA format item 9.a of the EA. In EA format item 9.b it should be specifically stated whether the natural resource is subject to the U.S. ESA/CITES. For natural resources covered under CITES, CDER may request copies of relevant permits.

VI. FOREIGN MANUFACTURING FACILITIES

Executive Order 12114, "Environmental Effects Abroad of Major Federal Actions," directs FDA to consider the environmental effects of approving drug product applications on the environment outside the United Sates. The responsible company official at each of the foreign facilities should certify that the manufacturing facilities are: 1) in compliance with all local and national environmental laws; 2) in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and 3) that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws. The statement should be signed and dated by the responsible company official and, if not in English, a certified English translation should be provided. FDA will request additional information if such information is needed to evaluate environmental effects outside the U.S.

VII. DRUG MASTER FILES

CDER does not take action on DMF's, *i.e.,* CDER does not approve or disapprove submissions to a DMF (21 CFR § 314.420(a)). Therefore, NEPA does not apply and no environmental assessment needs to be submitted for a DMF. However, CDER does take action on applications that incorporate by reference information regarding the manufacture of the drug substance or proprietary drug substance intermediates that may be submitted in Type II DMF's. In these instances, the drug product applicant should include the environmental assessment information for the manufacture of drug substance or proprietary drug substance intermediates in the EA if an EA or AEA is required for their particular application. The DMF holder may be the drug product applicant or an independent manufacturer who may want to limit the applicant's access to proprietary manufacturing information. The non-confidential information regarding the manufacture of the drug substance or proprietary drug substance intermediates should be included in the EA summary document. A DMF reference may be provided for the information which is defined as confidential in this guide (*e.g.,* substances expected to be emitted, EA format item 6.a) although this information must be summarized to the extent possible and included in the EA for public release. CDER prefers that copies of confidential information from DMF's be submitted in the EA by the drug product applicant as a confidential appendix, whenever possible, to expedite review of the EA. If a letter of authorization is provided to reference confidential information in a DMF, the specific information which is being referenced, and the submission date and page number where the information can be located, should be identified. References to DMF's should be included in a confidential appendix since such references are considered confidential commercial information under FOIA.

VIII. REFERENCES

A. Zeeman, M. and Gilford, J., "Ecological Hazard Evaluation and Risk Assessment Under EPA's Toxic Substances Control Act (TSCA): An Introduction," *Environmental Toxicology and Risk Assessment, ASTM STP 1179*, Wayne G. Landis, Jane S. Hughes, and Michael A. Lewis, Eds., American Society for Testing and Materials, Philadelphia, 1993, pp. 7-21.

B. Rand, Gary and Petrocelli, Sam., *Fundamentals of Aquatic Toxicology*, Hemisphere Publishing Corporation, 1987.

Submitted by:

_____

Nancy B. Sager
Acting Supervisor, Environmental Assessment Team

Approved by Director, Office of Pharmaceutical Science:

_____

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

ATTACHMENT A

FORMAT

AEA's:

Infrequent Use:

Complete EA format items 1 - 6 and 12 - 14. Documentation of EA format items 7 - 11 and 15 is ordinarily not required.

Naturally Occurring Substances:

Complete EA format items 1 - 6.d and 7.e - 15, while relying on available information for EA format items 7 and 8 (see 21 CFR § 25.31a(b)(5) for additional guidance).

Products Approved by EPA:

Complete EA format items 1 - 15, while relying on information in studies submitted to other federal or state agencies for items 7, 8 and 15 (see 21 CFR § 25.31a(b)(6) for additional guidance).

EA's: Generally, complete EA format items 1 - 15. If the Tier 0 approach is used, information in EA format items 7 - 11 and 15 may not be needed.

EA FORMAT ITEMS 1-15

1. Date
2. Name of Applicant/Petitioner
3. Address
4. Description of Proposed Action
- **a. Requested Approval**
- **b. Need for Action**
- **c. Production Locations**
- **d. Locations of Use**
- **e. Disposal Sites**

5. Identification of Chemical Substances that are the Subject of the Proposed Action
- **a. Nomenclature**
  - **i. Established Name (U.S. Adopted Name - USAN)**
  - **ii. Brand/Proprietary Name**
  - **iii. Chemical Names**

- **(1) Chemical Abstracts (CA) Index Name**
- **(2) Systematic Chemical Name**

b. Chemical Abstracts Service (CAS) registration number
c. Molecular Formula
d. Molecular Weight
e. Structural (graphic) Formula
f. Physical Description
g. Additives
h. Impurities

6. Introduction of Substances into the Environment

a. Substances Expected to be Emitted
b. Controls Exercised
c. Citation of and Statement of Compliance with Applicable Emission Requirements
d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements
e. Expected Introduction Concentrations

- **i. Expected Introduction Concentration from Use**
- **ii. Expected Introduction Concentration from Disposal**

7. Fate of Emitted Substances in the Environment

(Note: the following are included in the text of the guidance as section III.D.7.d.i-v)

a. Identification of Substance(s) of Interest
b. Physical/Chemical Characterization

- **i. Water Solubility**
- **ii. Dissociation Constant(s)**
- **iii. Octanol/Water Partition Coefficient**
- **iv. Vapor Pressure or Henry's Law Constant**

c. Environmental Depletion Mechanisms
d. Expected Environmental Concentration (EEC)
e. Summary

8. Environmental Effects of Released Substances
9. Use of Resources and Energy

a. Natural Resources and Energy
b. Effect on Endangered or Threatened Species
c. Effect on Property Listed in or Eligible for Listing in the National Register of Historic Places

10. Mitigation Measures
11. Alternatives to the Proposed Action
12. List of Preparers
13. Certification
14. References

15. Appendices

ATTACHMENT B

SAMPLE EMISSION PERMIT TABLE

PERMITS FOR XXXX FACILITY			
EMISSION	AUTHORIZING AGENCY	PERMIT #	EXPIRATION DATE

ATTACHMENT C

SAMPLE DATA SUMMARY TABLE

PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility[1]	
Dissociation Constant(s)	
Octanol/Water Partition Coefficient (Log K_{ow})[1]	
Vapor Pressure or Henry's Law Constant	
Sorption/Desorption (K_{oc})[1]	
DEPLETION MECHANISMS	
Hydrolysis	
Aerobic Biodegradation	
Soil Biodegradation	
Photolysis	
Metabolism	
ENVIRONMENTAL EFFECTS[2]	
Microbial Inhibition	
Acute Toxicity	
Chronic Toxicity	

[1]Depending on dissociations constant(s), water solubility and octanol/water partition coefficient may have to be determined at pH 5 and 9, in addition to pH 7 or K_{oc} may have to be determined in acidic and/or alkaline soil in addition to neutral soil. See section III.D.7.d.ii for guidance.

[2]Identify organism(s) and report results,*e.g.,* NOEC, MIC, $EC_{50,}$ LC_{50} in ppm of active moiety.

ATTACHMENT D

CONFIDENTIAL/NON-CONFIDENTIAL

EA FORMAT ITEM	SUBSECTION	NON-CONFIDENTIAL	CONFIDENTIAL
1.Date	***	X	
2. Name of Applicant/Petitioner	***	X	
3. Address	***	X	
4. Description of Proposed Action	a. Requested Approval	X	
	b. Need for Action	X	
	c. Production Locations	* Names and addresses of facilities released under FOIA procedures	* Names and address of facilities excluded from public release under FOIA procedures
	d. Locations of Use	X	
	e. Disposal Sites	* Disposal method(s) * Statement regarding licensing/ permitting of disposal facilities	* Specific information regarding contract disposal companies/facilities

ATTACHMENT D

CONFIDENTIAL/NON-CONFIDENTIAL

EA FORMAT ITEM	SUBSECTION	NON-CONFIDENTIAL	CONFIDENTIAL
5. Identification of Chemical Substances that are the Subject of the Proposed Action	a. Nomenclature	X	
	b. CAS Number	X	
	c. Molecular Formula	X	
	d. Molecular Weight	X	
	e. Structural Formula	X	
	f. Physical Description	X	
	g. Additives	* General discussion or reference to confidential appendix	* Specific information
	h. Impurities	* General discussion or reference to confidential appendix	* Specific information

ATTACHMENT D

CONFIDENTIAL/NON-CONFIDENTIAL

EA FORMAT ITEM	SUBSECTION	NON-CONFIDENTIAL	CONFIDENTIAL
6. Introduction of Substances into the Environment	a. Substances Expected to be Emitted	* General discussion or reference to confidential appendix	* Specific information
	b. Controls Exercised	X	
	c. Citation/Statement of Compliance	* Citations * Signed statements for facilities released under FOIA procedures * General statements and reference to confidential appendix for facilities not released under FOIA procedures	* Signed statements for facilities excluded from release under FOIA procedures
	d. Effect of Approval on Compliance with Current Emission Requirements	X	
	e. Expected Introduction Concentrations	* Summary discussion	* Specific calculations * 5th year production estimates

ATTACHMENT D

CONFIDENTIAL/NON-CONFIDENTIAL

EA FORMAT ITEM	SUBSECTION	NON-CONFIDENTIAL	CONFIDENTIAL
7. Fate of Emitted Substance in the Environment	a. Identification of Chemical Compounds of Interest	* Substances expected to enter or exist in the environment. * Summary discussion of toxicity/activity of predominant SRS's relative to the parent (active) compound	* Specific toxicology/ pharmacological activity data for SRS's
	b. Physical/ Chemical Characterization	* Test results	* Test reports
	c. Depletion Mechanisms	* Test results	* Test reports
	d. Expected Environmental Concentrations	* Summary discussion	* Specific information that would disclose production volumes
	e. Summary	X	
8. Environmental Effects of Released Substances	***	* Test results and summary discussion	Test reports

ATTACHMENT D

CONFIDENTIAL/NON-CONFIDENTIAL

EA FORMAT ITEM	SUBSECTION	NON-CONFIDENTIAL	CONFIDENTIAL
9. Use of Resources and Energy	a. Natural Resources & Energy	X	
	b. Effect on Endangered or Threatened Species	X	
	c. Effect on Property Listed in or Eligible for Listing in the National Register of Historic Places	X	
10. Mitigation Measures	***	X	
11. Alternatives to the Proposed Action	***	X	
12. List of Preparers	***	X	
13. Certification	***	X	
14. References	***	X	

ATTACHMENT D

CONFIDENTIAL/NON-CONFIDENTIAL

EA FORMAT ITEM	SUBSECTION	NON-CONFIDENTIAL	CONFIDENTIAL
15. Appendices	***	For example: * Material Safety Data Sheets * Certifications or statements of compliance from manufacturers that have been disclosed in the EA summary document * Referenced articles not generally available or which are used to support specific claims in the EA document * Data summary table	For example: * Confidential production information * Test reports * Identification of facilities that are considered confidential under FOIA procedures and any other information which would disclose this information (e.g., statement of compliance) * Letters of authorization to DMF's

ATTACHMENT E

GLOSSARY OF TERMS

Active Moiety: The molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance (21 CFR § 314.108(a)). The active moiety is the entire molecule or ion, not the "active site."

Bioaccumulation: The process by which industrial waste, chemicals and other substances gradually accumulate in living tissue.

Bioconcentration: The process by which industrial waste, chemicals and other substances accumulate directly from water into and onto aquatic organisms.

Drug product: A finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more ingredients (21 CFR § 314.3(b)).

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR § 314.3(b)).

Expected environmental concentration (EEC): The expected concentration of the active moiety or other structurally related substance of interest that organisms would be exposed to in the environment (*e.g.,* surface water) after consideration of spatial or temporal concentration or depletion factors such as dilution, degradation, sorption, bioaccumulation. This is sometimes referred to as the predicted environmental concentration (PEC).

Expected introduction concentration (EIC) for disposal: The expected introduction concentration of the active moiety which may enter the environment due to disposal. Depletion mechanisms that occur prior to introduction into the environment may be considered in the calculation.

Expected introduction concentration (EIC) for use: The expected introduction concentration, based on fifth year marketing estimates, of the active moiety which may enter the environment due to use. Depletion mechanisms that occur prior to introduction into the environment and human metabolism may be considered in the calculation.

Half-life ($t_{½}$): Time required to reduce by one-half the concentration of a material.

Lowest observed effect concentration (LOEC): The lowest concentration of a material used in a toxicity test that has a statistically significant adverse effect on the exposed population of the test organisms as compared with the controls.

Maximum expected environmental concentration (MEEC): The expected introduction concentration (EIC) or expected environmental concentration (EEC), whichever is greater.

Median effective concentration (EC_{50}): The concentration of material to which organisms are exposed that is estimated to be effective in producing some sublethal response in 50% of the test organisms. The EC_{50} is usually expressed as a time-dependent variable (*e.g.,* 24 hour EC_{50}).

Median lethal concentration (LC_{50}): The concentration of material to which organisms are exposed that is estimated to be lethal to 50% of the test organisms. The LC_{50} is usually expressed as a time-dependent variable (*e.g.,* 24 hour LC_{50}).

Minimum inhibitory concentration (MIC): The lowest concentration of a chemical that inhibits the visible growth of the test organisms.

No observed effect concentration (NOEC): The highest concentration of a material used in a toxicity test that has no statistically significant adverse effect on the exposed population of test organisms as compared with the controls.

Octanol/water partition coefficient (K_{ow}): The ratio of a chemical's solubility in n-octanol and water at equilibrium; also expressed as P. A measurement of a drug's lipophilicity and an indication of its ability to cross cell membranes. The logarithm of P or K_{ow} is used as an estimate of the tendency of the chemical to bioaccumulate or adsorb to soil or sediments.

Parts per billion (ppb): One unit of chemical (usually expressed as mass) per 1,000,000,000 (10^9) units of medium (*e.g.,* water) or organism (*e.g.,* tissue) in which it is contained. For water 1 µg/L = 1 ppb; for tissue 1 µg/kg = 1 ng/g = 1 ppb.

Parts per million (ppm): One unit of chemical (usually expressed as mass) per

1,000,000 (10^6) units of medium (*e.g.,* water) or organism (*e.g.,* tissue) in which it is contained. For water 1 mg/L = 1 ppm; for tissue 1 mg/kg = 1 µg/g = 1 ppm.

Parts per trillion (pptr): One unit of chemical (usually expressed as mass) per 1,000,000,000,000 (10^{12}) units of medium (*e.g.,* water) or organism (*e.g.,* tissue) in which it is contained. For water 1 ng/L = 1 pptr; for tissue 1 ng/kg = 1 pptr.

Primary packaging operations: Manufacturing operations which result in the drug product being placed into the immediate container (*i.e.,* container which is in direct contact with the drug product).

Secondary packaging operations: All packaging operations other than the primary packaging operation.

Soil or sediment/water partition coefficient (K_{oc}): The ratio of chemical adsorbed per unit weight of organic carbon in soil or sediment to the concentration of the chemical in solution at equilibrium.

"Substance that occurs naturally in the environment": In the context of § 25.31a(b)(5) this refers to organic or inorganic drug substances, whether obtained from a natural resource or synthesized, that will exist in the environment in the same form as the substance found naturally in the flora, fauna, atmosphere, water or soil.

Toxicity: The inherent potential or capacity of a material to cause adverse effects in a living organism.

Type 1 NDA[2]**:** A new drug application (NDA) for a drug for which the active moiety (present as the unmodified base [parent] compound, or an ester or a salt, clathrate, or other noncovalent derivative of the base [parent] compound) has not been previously approved or marketed as the active moiety in the United States for use in a drug product, either as a single ingredient or as part of a combination product or as part of a mixture of stereoisomers.

---

[2]For complete definitions of Type 1-7 NDA's see Center for Drug Evaluation and Research, Staff Manual Guide, 4820.3, “Drug Classification and Priority Review.”

Type 2 NDA: A new drug application (NDA) for a drug for which the active moiety has been previously approved or marketed in the United States but for which the particular ester, or salt, clathrate, or other noncovalent derivative or unmodified base (parent) compound has not yet been approved or marketed in the United States, either as a single ingredient, part of a combination product, or part of a mixture of stereoisomers.

Type 3 NDA: A new drug application (NDA) for a new dosage form or formulation, including a new strength, where the drug has already been approved or marketed in the United States by the same or another manufacturer. The indication may be the same as that of the already marketed drug product or may be new.

Type 4 NDA: A new drug application (NDA) for a drug product containing two or more active moieties that have not been previously approved or marketed together in a drug product by any manufacturer in the United States. The new product may be a physical or a chemical (ester or non-covalent) combination of two or more active moieties.

Type 5 NDA: A new drug application (NDA) for a drug product that duplicates a drug product already approved or marketed in the United States by another firm.

Type 6 NDA: A new drug application (NDA) for a drug product that duplicates a drug product (same active moiety, same salt, same formulation, or same combination) already approved or marketed in the United States by the same or another firm except that it provides for a new indication.

Type 7 NDA: The first new drug application (NDA) for a drug product containing one or more drugs marketed at the time of application or in the past without an approved NDA.